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EXAMINER	
KRSEK STAPLES, J	
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DATE MAILED: 04/07/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Amd A + Election

☒ This application has been examined ☒ Responsive to communication filed on 1-17-95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-7, 10-31 are pending in the application.
   Of the above, claims 11-21 are withdrawn from consideration.
2. ☒ Claims 8+9 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-7, 10+22-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Applicant's election without traverse of Group I, claims 1-10 in Paper No. 6 is acknowledged. As stated in the Restriction Requirement, Group IV, claims 22-31, drawn to a pharmaceutical composition will be examined with the elected method Group I. Claims 8 and 9 have been cancelled. Claims 11-21 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

The disclosure is objected to because of the following informalities:

It appears that Bacille Calmette-Guerin should be Bacillus Calmette-Guerin on pages 14, 18 and 28 of the specification and in claim 28.

The abbreviations "DFS" and "TS" on page 42 relating to the results of the Kaplan Meir analysis are not defined.

Appropriate correction is required.

The specification is also objected to because page 24 describes a graph which compares the percent of tumor free patients treated with DNP vaccine and non-haptenized control vaccine. However, the rest of page 24 is blank and the table located on page 25 is a schedule of DNP-Vaccine Therapy of Melanoma and is not the graph of the patient data.

Claims 1-7, 10 and 22-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 22 recite tumor cells and tumor cell extracts as being the irradiated composition. Claims 2 and 23 recite "wherein said tumor cells and extracts are selected from cells and extracts which are autologous, allogenic, or stem cells". It is not clear how tumor cells or tumor cell extracts can also be stem cells.

In claim 1 the term "haptenized therapeutically effective amount of an irradiated composition" is vague because it is not clear whether the hapten is conjugated to the irradiated composition or whether it is separately added to the composition.

In claims 1, 4, 22, 30 and 31 the term "tumor cell extracts" is vague. The specification states that "Chemical or cellular extracts may be isolated from the cell surface". The specification also defines these extracts as "a peptide isolated from cancerous cells" or "proteins encoded by cancer oncogenes or mutated anti-oncogenes" or "chemicals unique or substantially specific to a particular type of cancer" (see page 12). Because the characteristics and properties of these chemicals and the structures of the proteins and peptides have not been defined, it is not clear what is encompassed by the phrase "tumor cell extracts".

Claims 22, 26, and 27 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 22 recites a pharmaceutical composition selected from the group consisting of tumor cells, tumor cell extracts and a mixture of tumor cells and tumor cell extracts, mixed with an adjuvant. The language of this claim is closed and does not include additional components.

Because claims 26 and 27 recite "the composition of claim 22 further comprising a hapten", the addition of a hapten to claim 22 does not further limit the composition of claim 22.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The claimed invention is directed to a method and a pharmaceutical composition for treating cancer including melanoma, lung cancer, colon cancer, breast cancer, kidney cancer and prostate cancer. The specification specifically teaches a melanoma vaccine and describes immune responses to the melanoma vaccine and clinical results (p 19-43). While the specification states that cancers treatable with the present invention include those listed above, the specification does not teach how to select tumor cells or extracts which would be effective in treating these other cancers.

The specification states that extracts of the present invention comprise a peptide isolated from cancerous cells and state that chemical or cellular extracts may be isolated from the cell surface (p 12). The specification discloses that cancer specific extracts include peptides binding to the major histocompatibility complex, other cell-surface associated proteins, proteins encoded by cancer oncogenes or mutated oncogenes. The specification also states that the extract

comprises chemicals unique or substantially specific to a particular type of cancer (p 12). The specification cites Rotzschke et al as teaching the isolation of peptides form cells and states that the fractions obtained by this method are screened for immunological activity by allowing them to bind to autologous B lymphoblastoid cells which are then tested for ability to stimulate melanoma-specific T lymphocytes (paragraph bridging pages 16-17).

The specification does not characterize such extracts including peptides, products of oncogenes, or other chemicals. The method of Rotzschke et al describes the isolation of viral peptides from major histocompatibility complex class I molecules in tumor cells infected with virus. The peptides isolated in this procedure are not specifically tumor-derived peptides but rather are viral peptides. Therefore, the specification does not provide guidance for the isolation and identification of tumor cell extracts as defined above. The specification also does not provide guidance for treating the other cancers listed above using tumor cells or tumor cell extracts.

The treatment of cancer using tumor antigens is unpredictable as discussed by Bystryn. Bystryn teaches that tumor antigens selected for therapy must a) be able to induce clinically effective immune responses in humans; b) be expressed on the tumor to be treated; c) be located at a site on the tumor where they can interact with immune effector mechanisms (p 83, paragraph bridging columns 1 and 2). Bystryn also teaches that other variables such as the tumor load of the patient may also play a role in the effectiveness of the tumor antigen for therapy (p 85, column 1).

The specification does not provide guidance for selecting specific tumor antigens which meet this criteria and would be expected to function as a therapeutic agent against cancers other

than melanoma when administered in the claimed vaccine composition. The use of autologous melanoma cells for the treatment of melanoma cannot be extrapolated to the use of tumor cells and tumor cell extracts to treat other forms of cancer. Bystryn teaches that for cancer immunotherapy to be effective the immune responses induced must be directed to antigens being expressed by the tumor being treated. Bystryn discloses the pattern of tumor antigens expressed by cancers of the same histological type in different individuals is variable. Bystryn also teaches that there is variation in the pattern of tumor antigens expressed by different tumor cells of the same histological type in the same individual (p 84 paragraph 1). Furthermore, the profile of tumor antigens expressed by a tumor during its progression may be altered by the immune response of the host as a result of antigenic modulation. Bystryn also discloses that as a consequence of this variability it is unlikely that vaccines prepared from a single tumor antigen will be effective against a broad range of tumors of the same histological type and for the same reason autologous vaccines may not be effective against other tumor cells in the same patient (p 84, column 1).

In a review article by Finn, several potential tumor antigens are discussed and Finn states that the likelihood of finding antigens on tumors that will truly be tumor-rejection antigens is great. But as of 1993, these antigens had not yet been identified as Finn summarized in the conclusion of the paper:

> The term 'tumor-rejection antigens' used in the title of this review does not accurately reflect the nature of the molecules discussed. In fact every author whose work was reviewed has carefully avoided using this term, because very few molecules identified so far can be implicated in tumor rejection. The term is used here to

> primarily support the notion that many such molecules exist....The research community recognizes that having a tumor-specific antigen or peptide does not guarantee that anti-tumor responses will be generated *in vivo*, or that these responses will prevent or inhibit tumor growth. Given the diversity of the molecules reported this year, and the potential diversity of those that will be found in the near future, the likelihood of finding antigens on tumors that will truly be tumor-rejection antigens is great".

The melanoma vaccine disclosed in the specification consists of irradiated autologous melanoma cells. The specification does not teach that the administration of melanoma vaccine or other cancer vaccine using allogeneic tumor cells would be effective in treating cancer. Hellstrom et al disclose that allogeneic tumor cells or extracts used as immunogens may not induce cytotoxic lymphocyte (CTL) response because there may be a lack of major histocompatibility complex (MHC) matching between the immunogen and the patient's lymphocytes (p 29, paragraph 7). For the reasons discussed above, a vaccine composition for the treatment of one type of cancer cannot be extrapolated to other types of cancer and the effectiveness of either allogenic or autologous tumor antigens in treating cancer also unpredictable.

The sentence bridging pages 27-28 in the specification states that "All vaccines were DNP-conjugated and mixed with Bacille Calmette-Guerin" (BCG). The method claims have recently been amended to exclude the recitation of an adjuvant. However, it appears that including BCG may be a critical method step. Livingstone et al disclosed that in a melanoma vaccine using the GM2 ganglioside, antibody responses were not induced unless BCG was added to the purified GM2 vaccine (p 2913, paragraph bridging columns 1 and 2). Livingstone et al

also state that "Adjuvants and pretreatment with low doses of cyclophosphamide were important factors in the mouse studies, and results of the present human trials indicate their importance in melanoma patients" (p 2914, column 1). Hoover et al also used BCG as an adjuvant in a colorectal cancer vaccine and states that the correct amount of the appropriate adjuvant (i.e. BCG) was a critical condition of the success of the immunotherapy (p 1242, column 1, paragraph 2). The specification also does not provide guidance for using a pharmaceutical composition in which the melanoma cells are not irradiated. It would be expected that irradiation would be necessary to prevent the cells from growing following injection. Based on the teachings above, one of skill in the art would not expect that the claimed method would be effective in treating melanoma without specifically including BCG as demonstrated in the specification and one of skill in the art would not expect that the claimed composition would be effective without using irradiated tumor cells.

As stated above, the specification discloses that all vaccines were DNP-conjugated and that the control group of patients received non-haptenized autologous melanoma vaccine (p 29). Therefore, the specification specifically teaches non-haptenated cells and an adjuvant, as recited in the composition claim, do not prevent against melanoma. The specification also does not provide guidance for the addition of a hapten to the composition which is not chemically linked to the tumor cell. Because haptens are only immunogenic when bound to a carrier, one of skill in the art would not expect that the addition of free hapten to tumor cells or tumor cell extracts would induce the same type of immune response as the DNP-conjugated compositions disclosed in the specification.

Claims 1-7, 10 and 22-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-6 and 22-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,290,551. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent No. 5,290,551 is drawn to a vaccine useful for the treatment of melanoma comprising irradiated autologous melanoma cells conjugated to a hapten and an adjuvant. Claim 2 of U.S. Patent No. 5,290,551 is drawn to a method for treating melanoma comprising administering cyclophosphamide followed by the above composition. Claims 1-6 are drawn to a method for treating cancer comprising administering cyclophosphamide and irradiated tumor cells which include autologous melanoma cells and a hapten. Claims 22-29 are drawn to a pharmaceutical composition containing tumor cells which include melanoma cells, a hapten and an adjuvant. Therefore, although claim 1 of this application does not specifically recite an adjuvant, it may comprise an adjuvant and therefore the claims of the instant application contain all of the limitations of claims 1 and 2 of U.S. Patent No. 5,290,551 and are not patentably distinct.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided

the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6 and 22-29 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Murphy et al.

Murphy et al disclose a method for treating melanoma comprising administering to a patient a therapeutically effective amount of cyclophosphamide and administering a therapeutically effective amount of autologous, irradiated dinitrophenol (DNP)-conjugated melanoma cells mixed with the adjuvant BCG. Murphy et al also disclose a pharmaceutical composition of autologous (DNP)-conjugated melanoma cells mixed with BCG. While claim 1 does not specifically recite the administration of an adjuvant, because it recites "comprising" an including an adjuvant is within the scope of the claim.

Claims 1-7 and 22-29 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Berd et al (Proc Am Assoc Cancer Res Annu Meet 30: 382, 1990).

Berd et al disclose a method for treating melanoma comprising administering to a patient a 300 mg/M^2 of cyclophosphamide and administering a therapeutically effective amount of autologous, irradiated dinitrophenol (DNP)-conjugated melanoma cells mixed with the adjuvant BCG. Berd et al also disclose a pharmaceutical composition of autologous (DNP)-conjugated melanoma cells mixed with BCG. While claim 1 does not specifically recite the administration of an adjuvant, because it recites "comprising" an including an adjuvant is within the scope of the claim.

Claims 22-25, 28 and 29 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Berd et al (AD).

Berd et al disclose a pharmaceutical composition consisting of autologous melanoma tumor cells mixed with Bacillus Calmette-Guerin adjuvant (p 2573, column 2 and p 2572).

Claims 22-24, 28 and 30 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Pattillo.

Pattillo discloses a pharmaceutical composition consisting of either autologous or allogenic tumor cell extracts, including extracts from breast tumor cells, mixed with the immunological adjuvant BCG (p 810, column 2, paragraph 3 and p 819, column 1, paragraph 4).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1 and 10 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al or Murphy et al in view of Geczy et al.

Berd et al and Murphy et al disclose a method for treating melanoma comprising sensitizing the patient with a therapeutically effective amount of dinitrochlorobenzene (DNCB) then administering a therapeutically effective amount of cyclophosphamide followed by a therapeutically effective amount of autologous, irradiated dinitrophenol (DNP)-conjugated melanoma cells mixed with the adjuvant BCG. Neither Berd et al or Murphy et al disclose administering 1-fluoro-2,4-dinitrochlorobenzene rather than DNCB.

Geczy et al teach that halogenated dinitrobenzenes such as 1-chloro- and 1-fluoro-2,4,-dinitrobenzene are commonly used to elicit delayed hypersensitivity (p 189 paragraph 1). It would have been obvious to use either 1-fluoro-2,4,-dinitrobenzene or DNCB in the method taught by Berd et al and Murphy et al because both of these chemicals are halogenated dinitrobenzenes with

a similar structure and they perform the same function. Therefore, they are considered functionally equivalent and both would be expected to sensitize a patient to DNP.

Claims 1-7, 10, and 22-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Berd et al in view of Fujiwara et al (AQ) and Fujiwara et al (AS) and Geczy et al.

Berd et al teach a method of treating melanoma comprising administering 300mg/M^2 cyclophosphamide and irradiated autologous melanoma cells mixed with BCG (p 2572-2573). Berd et al does not teach the administration of tumor cells haptenized with DNP nor does Berd et al teach sensitizing the patient with 1-fluoro-2,4-dinitrochlorobenzene.

Fujiwara et al (1980) teach that strong *in vitro* cytotoxic potential and *in vivo* tumor growth inhibition directed against unmodified tumor cells can be generated by first priming mice to generate hapten-reactive amplifier cells and then immunizing them with hapten-coupled tumor cells (p 867, column 2, paragraph 1). Fujiwara et al teach using trinitrophenol (TNP) as a hapten.

Fujiwara et al (1984) teach that TNP-reactive T cell responses can be induced by exposing the skin of mice to trinitrochlorobenzene (TNCB) (p 510, paragraph 3).

Geczy et al teach that halogenated dinitrobenzenes such as 1-chloro- and 1-fluoro-2,4,-dinitrobenzene are commonly used to elicit delayed hypersensitivity (p 189 paragraph 1).

It would have been obvious to one of ordinary skill in the art to conjugate the melanoma cells in the method taught by Berd et al to a hapten and to administer an agent to prime the patient to generate hapten-reactive amplifier cells in order to strengthen tumor growth inhibition

as taught by Fujiwara et al. Because dinitrophenyl and trinitrophenyl are both haptens and are structurally similar it would have been obvious to use either as a hapten to conjugate to the tumor cell because they would be functionally equivalent. In addition, it would have been obvious to use 1-fluoro-2,4-dinitrochlorobenzene as the priming agent because fujiwara et al teach that TNP-reactive T cell responses can be induced by topical exposure to TNCB and both 1-fluoro-2,4-dinitrochlorobenzene and TNCB are halogenated dinitrobenzenes with a similar structure and they perform the same function as taught by Geczy et al. Therefore, they are considered functionally equivalent and both would be expected to sensitize a patient to a hapten such as dinitrophenyl or trinitrophenyl.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie K. Staples whose telephone number is (703) 305-7556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 305-7939. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

JKS
Julie K. Staples, Ph.D.
March 27, 1995

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180